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RHEUMATOID ARTHRITIS

First face-off in RA biologic therapy declared a draw

Hard data to inform evidence-based treatment decisions in rheumatoid arthritis (RA) are difficult to amass in the flexible arena of modern clinical trial design. Now, 1-year findings from the first fully-powered head-to-head study of biological DMARD therapy in patients with RA supply essential information for clinicians facing such choices.

Published by Michael Weinblatt and colleagues in *Arthritis & Rheumatism*, the data are from an ongoing phase IIIb study assessing the relatively new option of subcutaneous abatacept therapy versus the more established agent adalimumab, also delivered subcutaneously, both given with background methotrexate. "The results demonstrate that the two treatments are virtually identical in efficacy," says RA expert Ronald van Vollenhoven, of the Karolinska Institute, Sweden, who was not involved in the trial.

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The primary outcome measure was the proportion of patients fulfilling the American College of Rheumatology (ACR) criteria for 20% improvement (ACR20) at 1 year; secondary measures included ACR50 and ACR70 rates, scores of disease activity, physical function and fatigue, and radiographic assessment of erosions and joint-space narrowing. Participants in the study—646 patients with active RA despite methotrexate therapy, and with no experience of biological DMARDs—were randomly assigned to receive either weekly abatacept (125 mg) or fortnightly adalimumab (40 mg) doses.

In the abatacept group the 1-year ACR20 response rate was 64.8% (95% CI 59.5–70.0), as compared with 63.4% (95% CI 58.2–68.6) for adalimumab. The estimated between-group difference was 1.8%, with a 95% CI of –5.6–9.2, confirming the study hypothesis of noninferiority of subcutaneous abatacept to adalimumab.

Although investigators were blinded to the treatment assignment, patients were not, as the different regimens and presentations of the therapies would have made disguise impractical. Nevertheless, "this was a well-designed and well-conducted trial without major weaknesses," opines van Vollenhoven; "I don't think that the lack of complete blinding of the patients is likely to have biased the results."

Besides being the first head-to-head comparison of biologic therapy in RA, this trial is also the first to report radiographic data for the subcutaneous formulation of abatacept. Inhibition of erosive and joint-space narrowing progression was comparable between the treatments.

Unlike adalimumab, abatacept does not target the proinflammatory cytokine TNF; rather, it disrupts a T-cell co-stimulatory pathway. These differing modes of action mean that the observed similarity between the kinetics of the responses in the two groups was somewhat surprising. "Many clinicians have felt that abatacept acts more slowly than anti-TNF agents, and a previous study with intravenous abatacept and infliximab supported that view," explains van Vollenhoven. "To think that subcutaneous administration would work more rapidly than intravenous for the same medication might seem counterintuitive but is not altogether implausible pharmacologically," he continues, adding that trough concentration levels of adalimumab might be lower in patients receiving intravenous therapy than weekly injections.

Rates of adverse events and serious adverse events were similar for the two treatments, whereas local injection site reactions were less frequent with abatacept than adalimumab (3.8% versus 9.1%; 95% CI –9.13–1.62). Further data are needed to confirm whether either treatment has a safety advantage, some of which will emerge as this trial continues. The study authors note that the rates and types of adverse events are similar to previously reported clinical trial data, and that comparative trials are most informative on safety issues when they reflect the findings of larger safety databases.

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"For practicing rheumatologists these data would put subcutaneous abatacept rather firmly on equal footing with one of the two most widely used anti-TNF agents, making it a reasonable therapeutic choice for patients in need of a biologic treatment," says van Vollenhoven. One ironic aspect of proving the efficacy of abatacept, he notes, is that we are not yet entirely sure how the agent works. "I believe the final word on this has not yet been spoken," he concludes.

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Original article Weinblatt, M. E. *et al*. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis. *Arthritis Rheum*. doi:10.1002/art.37711

Further reading van Vollenhoven, R. F. Unresolved issues in biologic therapy for rheumatoid arthritis. *Nat. Rev. Rheumatol*. **7**, 205–215 (2011) | Woodrick, R. S. & Ruderman, E. M. Safety of biologic therapy in rheumatoid arthritis. *Nat. Rev. Rheumatol*. **7**, 639–652 (2011)